

Section 4: Contrast-induced AKI

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Chapter 4.1: Contrast-induced AKI: definition, epidemiology, and prognosis

BACKGROUND

Contrast-related acute kidney problems are frequent and occur in both ambulatory and hospitalized patients. Since there is accumulating evidence that many risk factors, preventive measures, and the immediate and long-term prognosis of these problems are common to the other causes of AKI, the Work Group believes that there is a need for a unifying definition for all forms of AKI and therefore proposes that the term contrast-induced acute kidney injury (CI-AKI) be used for patients developing AKI secondary to intravascular radiocontrast media exposure.

The literature on CI-AKI is predominantly related to AKI following iodinated contrast-media administration. As will be discussed in Appendix E, non-iodine contrast media—notably Gd-containing contrast media—may also occasionally induce AKI.

- 4.1: Define and stage AKI after administration of intravascular contrast media as per Recommendations 2.1.1–2.1.2. (Not Graded)**
- 4.1.1: In individuals who develop changes in kidney function after administration of intravascular contrast media, evaluate for CI-AKI as well as for other possible causes of AKI. (Not Graded)**

RATIONALE

Pending the validation of future biomarkers which would allow a more straightforward comparison and integration of CI-AKI in the overall framework of AKI, we suggest that the same criteria, using the changes in SCr concentrations and urine output be used as for the other forms of AKI. The Work Group is not aware of any pathophysiological or epidemiological reason why the definition and staging of CI-AKI should be different from the RIFLE/AKIN criteria. It should, however, be stressed that for the development of this guideline, the term contrast-induced nephropathy is widely used in the literature and usually defined as a rise in SCr of ≥ 0.5 mg/dl (≥ 44 μ mol/l) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure. This definition also consistently predicted major

adverse cardiovascular events after percutaneous coronary intervention.³⁸⁵ The Society of Urogenital Radiology used the same definition, but the creatinine changes were said to occur within 3 days after intravascular administration of contrast media without an alternative etiology.³⁸⁶ It should be recognized that, in a minority of cases, the peak increase of SCr may occur up until 5 days after contrast exposure. However, a recent prospective study³⁸⁷ showed that the percentage change of SCr 12 h after contrast vs. the basal value was the best predictor of CI-AKI ($P < 0.001$). A 5% increase of its value yielded 75% sensitivity and 72% specificity, with an area under the curve (AUC) of 0.80 and an OR of 7.37 (95% CI 3.34–16.23) for early detection. Furthermore, this 12-hour basal value strongly correlated with the development of renal impairment at 30 days ($P = 0.002$; sensitivity 87%, specificity 70%; AUC 0.85; OR 13.29; 95% CI 2.91–60.64).

It has been shown that substantial variation in SCr may occur from day to day in hospitalized patients who do not receive contrast-media injections.³⁸⁸ Depending on the threshold criterion for CI-AKI chosen, this variation can lead to rates of 6–35% of inpatients, not exposed to contrast media, who would be labeled as having CI-AKI had they received contrast media. The exact cause of this “hospital-induced nephropathy”³⁸⁹ is not known, but other studies have shown that AKI (various etiologies) is common in hospitalized patients.

The magnitude of the impact of the “background fluctuation of kidney function” in patients receiving iodinated contrast has not been prospectively studied, but a recent retrospective study compared the incidence of AKI among patients undergoing enhanced computed tomography (CT) with i.v. low-osmolar (iohexol) or iso-osmolar (iodixanol) contrast media to the AKI incidence among patients undergoing CT without contrast-media administration.³⁹⁰ The incidence of AKI (defined as an increase of SCr of 0.5 mg/dl [44 μ mol/l] or a $\geq 25\%$ decrease in eGFR within 3 days after CT) was similar in all three groups (two receiving contrast agents and one not) up to a baseline SCr level of 1.8 mg/dl (159 μ mol/l). A high incidence of “AKI” among control subjects undergoing noncontrast CT was thus identified. Given the results of this retrospective study, it is clear that AKI after i.v. administration

of iodine contrast media cannot be automatically attributed to the contrast agent, but may, in fact, reflect AKI from other causes, such as worsening underlying disease or drug toxicity. Therefore, the Work Group strongly recommends that individuals showing increases of SCr compatible with the definition of AKI after administration of intravascular contrast media be also evaluated for other possible causes of AKI.

In a study using cystatin C as an early marker for AKI, a cut-off cystatin C increase concentration of $\geq 10\%$ at 24 hours after contrast-media exposure was detected in 87 patients (21.2%), and was the best cut-off value for the early identification of patients at risk for CI-AKI with a negative predictive value of 100% and a positive predictive value of 39%. As in other cases of AKI, it appears that, in patients with CKD, cystatin C may be a useful marker for the early diagnosis of CI-AKI.

Epidemiology of CI-AKI

Keeping the above-mentioned problems of definition in mind, it is not surprising that the reported incidence of CI-AKI varies widely across the literature, depending on the definitions used, the patient population, and the baseline risk factors.

The impact of different definitions on the incidence of CI-AKI can be illustrated by the recent results of the Oxilan Registry.³⁹¹ In this registry, CI-AKI was defined as either a SCr increase > 0.5 mg/dl (> 44 μ mol/l), or a SCr increase $> 25\%$, or a decrease $> 25\%$ of eGFR, or the composite of all three definitions. The baseline SCr was 1.12 ± 0.3 mg/dl (99 ± 26.5 μ mol/l) and 24% had an eGFR < 60 ml/min. CI-AKI rates were 3.3% (SCr increase > 0.5 mg/dl [> 44 μ mol/l]), 10.2% (SCr increase $> 25\%$), 7.6% (eGFR decrease $> 25\%$), and 10.5% (composite), respectively.

It is accepted that, in patients with normal renal function—even in the presence of diabetes—the risk for CI-AKI is low (1–2%).³⁹² However, the incidence may be as high as 25% in patients with pre-existing renal impairment or in presence of certain risk factors, such as the combination of CKD and diabetes, CHF, advanced age, and concurrent administration of nephrotoxic drugs.³⁹³ CI-AKI was described as the third most common cause of new AKI in hospitalized patients (after decreased renal perfusion and nephrotoxic medications) and was responsible for 11% of cases.³⁹⁴

The epidemiology of *de novo* CI-AKI in critically ill patients is not known. In a group of 75 ICU patients with a normal baseline SCr who were exposed to CT scans with an i.v. low-osmolar contrast medium, an increase in SCr $> 25\%$ was recorded in 18% of the patients. There was no change of the SCr in a control group of patients undergoing CT scans but not receiving contrast media.³⁹⁵ This rather small study shows that in critically ill patients, even with an apparently “normal” renal function, i.v. administration of iodinated contrast media is associated with a significant incidence of CI-AKI.

It could be expected that radiological procedures performed in an emergency would be associated with an

increased risk of CI-AKI but, as recently summarized,³⁹⁶ the published evidence to support this premise is rather scarce.³⁹⁷

Prognosis of CI-AKI

Many studies have now shown that patients who develop CI-AKI have a greater risk for death or prolonged hospitalization, as well as for other adverse outcomes, including early or late cardiovascular events. The latter are more common after, for example, percutaneous coronary interventions (for review, see McCullough³⁹⁸). In a retrospective analysis including 27 608 patients who underwent coronary angiography at the University of Pittsburgh Medical Center during a 12-year period, discrete proportional odds models were used to examine the association between increases in SCr and 30-day in-hospital mortality and LOS, respectively. It appeared that small absolute (0.25–0.5 mg/dl [22 – 44 μ mol/l]) and relative (25–50%) increases in SCr were associated with risk-adjusted OR for in-hospital mortality of 1.83 and 1.39, respectively; larger increases in SCr generally were associated with greater risks for these clinical outcomes.³⁹⁹ Moreover, when patients with CI-AKI require dialysis, the mortality is higher compared to those not requiring dialysis. For example, in the study by McCullough *et al.*,⁴⁰⁰ the hospital mortality was 7.1% in CI-AKI and 35.7% in patients who required dialysis. By 2 years, the mortality rate in patients who required dialysis was 81.2%.

The more recent Cardiac Angiography in Renally Impaired Patients study⁴⁰¹—a large, multicenter, prospective, double-blind RCT of patients who had moderate to severe CKD and were undergoing cardiac angiography—also showed that the adjusted incidence rate ratio for adverse events was twice as high in those with CI-AKI. However, these data demonstrating a temporal association between CI-AKI and short or long-term prognosis do not establish a causal relationship, since most of the patients in these observational studies have underlying risk factors that, in addition to increasing the patient's risk of CI-AKI, can directly increase their overall risk for the complications studied. Finally, many of the retrospective studies may also have introduced selection bias for patients who presumably had a clinical reason for having their SCr concentration followed.

Data on the association between risk of ESRD and CI-AKI are scarce. In contemporary studies, CI-AKI requiring dialysis developed in almost 4% of patients with underlying renal impairment and 3% of patients undergoing primary percutaneous coronary interventions for acute coronary syndrome. However, only a small proportion of patients continued on chronic dialysis.^{402,403} Although CI-AKI requiring dialysis is relatively rare, the impact on patient prognosis is considerable, with high hospital and 1-year mortality rates (for a review, see McCullough³⁹⁸). Only one study⁴⁰⁴ reported the incidence of new CKD Stage 4–5 (eGFR < 30 ml/min) following percutaneous coronary interventions and found that this occurred in 0.3% of patients

with an eGFR > 30 ml/min at baseline and newly diagnosed kidney disease within 6 months after the procedure, and in 0.9% of patients with an eGFR > 60 ml/min at baseline. These percentages are higher than the estimated annual incidence of CKD at 0.17% that was found in a British general population cohort over a 5.5-year period of follow-up.⁴⁰⁵ Thus, careful long-term follow-up of SCr following contrast exposure is warranted.

RESEARCH RECOMMENDATION

- Large prospective RCTs examining the epidemiology of CI-AKI are needed, especially on long-term outcomes, with attention to controlling for confounders.

SUPPLEMENTARY MATERIAL

Appendix E: Risks with Gadolinium-Based Contrast Agents.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 4.2: Assessment of the population at risk for CI-AKI

At present, millions of doses of intravascular contrast media are being administered worldwide.^{406,407} Most of these radiological examinations are performed in ambulatory populations who do not need special preventive measures. However, contrast media are also increasingly used in an elderly population, many of whom have CKD and diabetes—the principal risk factors for CI-AKI. It is, thus, of utmost importance to screen the population at risk for CI-AKI.

4.2.1: Assess the risk for CI-AKI and, in particular, screen for pre-existing impairment of kidney function in all patients who are considered for a procedure that requires intravascular (i.v. or i.a.) administration of iodinated contrast medium. (Not Graded)

RATIONALE

Screening for pre-existing impairment of kidney function

Pre-existing renal functional impairment is the most important risk factor above all other risk factors for developing CI-AKI⁴⁰⁸ and screening for both acute and chronic kidney disease is highly recommended. There is no sharp GFR threshold below which the risk for CI-AKI is clearly increasing. Both the KDOQI guideline and KDIGO recommend that, in stable patients, an eGFR should be used.⁴⁰⁹

A CI-AKI Consensus Working Panel⁴¹⁰ agreed that the risk of CI-AKI becomes clinically important when the baseline SCr concentration is ≥ 1.3 mg/dl (≥ 115 μ mol/l) in men and ≥ 1.0 mg/dl (≥ 88.4 μ mol/l) in women, equivalent to an eGFR < 60 ml/min per 1.73 m². However, Bruce *et al.*³⁹⁰ showed that the incidence of “true” AKI became significant only between controls and contrast-media administered patients from a baseline SCr concentration of > 1.8 mg/dl (> 159 μ mol/l) onward. The CI-AKI Consensus Working Panel⁴¹⁰ recommended that precautions to reduce the risk should be implemented in patients with a baseline eGFR < 60 ml/min per 1.73 m². In light of more recent information, this threshold could probably be lowered to 45 ml/min per 1.73 m².

In many institutions, point-of-care SCr testing is present, and the results can be available quite fast. In places without point-of-care laboratories, the appropriate blood tests should

be requested, but an emergent imaging/intervention, where the benefit of very early imaging outweighs the risk of waiting, should not be delayed.

For its relative simplicity, only SCr is used at many hospitals to determine whether a patient is a candidate for intravascular contrast-media administration, but the thresholds used and the acceptable time between the determined SCr value and administration of contrast media to perform the radiology examination differs among radiology departments.

Risk-factor questionnaire

For outpatient radiological studies where renal function data are unavailable, a simple survey or questionnaire may be used to identify outpatients at higher risk for AKI in whom appropriate precautions should be taken.

Choyke *et al.*⁴¹¹ (Figure 13) used a questionnaire and could identify a high proportion of patients with normal SCr concentrations, and reduced by 67% the number of patients in whom SCr measurement was necessary before imaging studies.

The European Society of Urogenital Radiology³⁸⁶ recommends a risk-factor analysis based on the Choyke questionnaire to identify patients with a higher risk of abnormal renal function. The CI-AKI Consensus Working Panel⁴¹⁰ considered that a survey or questionnaire may be a useful guide for identifying patients at higher risk for CI-AKI compared to the general population.

Urinary protein screening

The CI-AKI Consensus Working Panel also supported the use of dipstick testing for urine protein as a rapid screen to identify patients who can undergo studies requiring contrast media without SCr measurement.⁴¹⁰ Of 310 patients with a negative urine protein test and no history of diseases potentially associated with renal impairment, none had a SCr level > 2.0 mg/dl (> 177 μ mol/l), and only 1% had a level > 1.7 mg/dl (> 150 μ mol/l).

Thus, the Work Group recommends that, when a recent SCr is not available, a simple questionnaire or a dipstick testing for urine protein may be useful for identifying pre-existing kidney disease. Risk stratification hinges on age, baseline kidney function, other comorbidities, and other risk factors.

In the past 3 months have you been told there may have been a change in your kidney function? Y/N

In the past 3 months have you been on any medications? Please list:

Have you used any over-the-counter pain relievers within the last 10 days? Y/N Please list:

In the past 3 months have you had any surgery? Y/N

Describe:

Do you feel dry or thirsty? Y/N

Circle one

*Have you ever been told you have kidney disease of any type?	Y	N
Please describe:		
*Have you had kidney surgery?	Y	N
*Do you have diabetes?	Y	N
Do you use insulin?	Y	N
Do you use metformin or glucophage?	Y	N
*Do you have hypertension, heart disease, or vascular disease?	Y	N
*Do you have gout?	Y	N
Do you have multiple myeloma?	Y	N
Have you ever had x-ray contrast media (dye) for CT, angiography, or IVP?	Y	N
Have you had contrast media within the last 3 days?	Y	N
Do you have any allergies to x-ray contrast media (dye)?	Y	N
Please describe:		
Have you received pretreatment with medication for this study?	Y	N
Do you have any allergies or asthma? Please describe:	Y	N

Figure 13 | Sample questionnaire. Asterisks denote questions with the highest association with abnormal renal function. Adapted from Choyke PL, Cady J, DePollar SL *et al.* Determination of serum creatinine prior to iodinated contrast media: is it necessary in all patients? *Tech Urol* 1998; 4: 65–69 with permission.⁴¹¹

Other risk factors of CI-AKI

Besides pre-existing kidney disease with renal function impairment, other risk factors for developing CI-AKI include diabetes, hypertension, CHF, advanced age, volume depletion, hemodynamic instability, use of concurrent nephrotoxic medications, and large volume or high osmolality of the contrast agent.^{408,412} Although there is doubt that diabetes by itself is an independent risk factor, in a patient with CKD it acts as a risk multiplier.³⁹⁸ Metabolic syndrome, prediabetes, and hyperuricemia have been identified as new risk factors for CI-AKI, while the use of ACE-I and angiotensin-receptor blockers (ARB), renal transplantation, diabetes mellitus with normal renal function, low-osmolar contrast media, multiple myeloma, female gender, and cirrhosis have been classified as conflicting risk factors for CI-AKI.⁴¹³ There are conflicting data on the impact of ACE-I or ARB but, overall, there is currently insufficient evidence to recommend discontinuation of these medications prior to contrast-media administration.

When possible, the administration of contrast media should be delayed in patients with circulatory collapse or CHF until their hemodynamic status is corrected. Repeated exposure should be delayed for 48 hours in patients without risk factors for CI-AKI, and for 72 hours in those with diabetes mellitus or pre-existing chronic renal dysfunction. If acute renal dysfunction develops after contrast-media administration, repeated exposure should preferably be delayed until the SCr level has returned to baseline levels.⁴¹⁴

Concurrent nephrotoxic medication—including, in particular, NSAIDs, aminoglycosides, amphotericin B, high

Table 15 | CI-AKI risk-scoring model for percutaneous coronary intervention

Risk factors	Integer score (calculate)
Hypotension	5
IABP	5
CHF	5
Age > 75 years	4
Anemia	3
Diabetes	3
Contrast-media volume	1 per 100 ml
SCr > 1.5 mg/dl (> 132.6 μmol/l)	4
or	
eGFR < 60 ml/min per 1.73 m ²	2 for 40–60 4 for 20–39 6 for < 20

Note: Low risk: cumulative score < 5; high risk: cumulative score > 16.

CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; SCr, serum creatinine. Reprinted from Mehran R, Aymong ED, Nikolsky E *et al.* A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; 44: 1393–1399 *et al.*,⁴¹⁸ copyright 2004, with permission from American College of Cardiology Foundation; accessed <http://content.onlinejacc.org/cgi/content/full/44/7/1393>

doses of loop diuretics, and antiviral drugs like acyclovir and foscarnet—should preferably be stopped. A recent study using a so-called forced euvolemic diuresis protocol including mannitol and furosemide led to a significantly increased risk of CI-AKI.⁴¹⁵ It can be advised that such strategy should be abandoned, and that furosemide therapy should preferably be stopped before angiography.

Risk models of CI-AKI

Most risk factors for CI-AKI can be detected by history-taking and physical examination, and the risk rises exponentially with the number of risk factors present.⁴¹⁶ Validated risk-prediction models using patient and procedural risk factors to assess for CI-AKI have been developed for patients undergoing percutaneous coronary intervention.^{417,418} For example, the Mehran risk model⁴¹⁸ is given in Table 15. The overall occurrence of CI-AKI in the development set of the score was 13.1% (range 7.5% to 57.3% for a low [≤ 5] and high [≥ 16] risk score, respectively); the rate of CI-AKI increased exponentially with increasing risk score. In the validation dataset, the increasing risk score was again strongly associated with CI-AKI (range 8.4% to 55.9% for the low and high risk score, respectively). These models can help in counseling about the risks of the procedure, selecting prophylactic interventions, and can also be used to characterize patients in studies of CI-AKI.

4.2.2: Consider alternative imaging methods in patients at increased risk for CI-AKI. (Not Graded)

RATIONALE

The selection and advantages and disadvantages of non-iodinated contrast media are beyond the scope of these guidelines. Detailed discussions of all these techniques can be found in radiology textbooks and the radiology literature. The Work Group suggests that, in patients at increased risk for CI-AKI, the risks and benefits of iodinated contrast-media administration should be discussed with the radiologist.

Because of the great relevance for the nephrologist, radiologist, and cardiologist of the side-effects of Gd chelates used in magnetic resonance imaging (MRI), a short overview of their nephrotoxicity is given here.

Nephrotoxicity of Gd chelates

Gd chelates are widely used as MRI contrast agents, and are considered to have a good overall safety profile. Early on, phase III trials and small studies in low-risk patients suggested a benign renal profile; however, more recent studies raised the possibility of nephrotoxicity, although it is not clear whether it approaches the incidence of AKI associated with iodine-containing contrast media. Gd-related AKI appears to be a risk in patients with advanced kidney disease, especially those with diabetic nephropathy.^{419,420} Perazella *et al.*⁴²⁰ have summarized studies showing Gd-induced nephrotoxic AKI compared to CI-AKI.^{421–425} Studies in patients with underlying kidney disease demonstrate the importance of renal clearance in determining the pharmacokinetic profile of Gd chelates.⁴²⁶ More details on the pharmacokinetics of Gd chelates and their dialyzability are provided in Appendix E.

Nephrogenic systemic fibrosis (NSF)

The risk of developing NSF with Gd, particularly in patients with severe AKI and CKD, is reviewed in detail in Appendix E. It should be noted here that the European Medicines Agency stated a contraindication for use of gadodiamide in patients with a GFR < 30 ml/min per 1.73 m², and issued a warning for its use in patients who have a GFR between 30 and 60 ml/min per 1.73 m² (EMA Public assessment report. http://www.esur.org/fileadmin/NSF/Public_Assessment_Report_NSF_Gadolinium_26_June_2007.pdf; last accessed January 5, 2012). The US FDA requested that vendors add warnings about the risk for developing NSF to the full prescribing information on the packaging for all Gd-containing contrast agents (gadopentetate dimeglumine, gadodiamide, gadoversetamide, gadoteridol, gadobenate dimeglumine).⁴²⁷ New labeling describes the risk for NSF following exposure to Gd in patients with a GFR < 30 ml/min per 1.73 m² and in patients with AKI of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period. Additional recommendations were recently proposed by Perazella⁴²⁰ and were endorsed by the Work Group:

- (a) Use of a macrocyclic chelate (gadoteridol in the USA), is preferred over linear chelates. The risk associated with the various Gd-containing agents is likely different. Gadodiamide, the linear nonionic chelate-based formulation, maintains the highest risk on the basis of epidemiologic data and animal studies. Gadopentetate, the linear ionic chelate-based product probably has a medium risk, less than the linear nonionic chelates but more than the macrocyclic chelates. Gadoteridol, the only FDA-approved macrocyclic chelate, maintains less risk. Clearly, high dosages and large cumulative dosages of all these agents will increase risk for NSF.
- (b) Demonstration of significant quantities of insoluble Gd in the skin of NSF patients, months after exposure to Gd-based contrast material and after extensive tissue processing, suggests that Gd might have undergone transmetallation *in vivo*. Supporting the importance of transmetallation, all NSF cases reported before 2009 have been associated with linear MRI contrast agents (for a review, see Kay⁴²⁸) that have inferior thermodynamic stability and a kinetic or conditional stability that favors transmetallation. However, a recent case of NSF in a dialysis patient after exposure to a macrocyclic chelate has been described,⁴²⁹ and at least two additional cases are known.⁴³⁰
- (c) Use the lowest dosage of the agent possible to achieve the image.
- (d) Avoid repeat exposures with Gd.
- (e) Consider performing IHD after the exposure (and the next 2 days) in patients who are already maintained on IHD, recognizing that there are no data that support prevention of NSF with this modality.

This recommendation is based on the pharmacokinetics of Gd and the theoretical benefit of removing it with IHD (>95% plasma clearance). PD clears these agents rather poorly.

SUPPLEMENTARY MATERIAL

Appendix E: Risks with Gadolinium-Based Contrast Agents.

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Chapter 4.3: Nonpharmacological prevention strategies of CI-AKI

There have been a large number of strategies/agents evaluated to prevent CI-AKI. Sterling *et al.*⁴³¹ have recently summarized most of these strategies and classified them as having either definitive, possible, or doubtful value. From the many strategies, these authors only retain parenteral volume expansion, minimizing contrast-media volume, use of low-osmolar and iso-osmolar contrast media, and administration of non-iodinated contrast media as strategies with definitive value. A recent comprehensive meta-analysis by Kelly *et al.*⁴³²—including RCTs that administered NAC, theophylline, fenoldopam, dopamine, iloprost, statins, furosemide, or mannitol, and covering studies up to November 2006—provides an excellent overview.

DOSE/VOLUME OF CONTRAST-MEDIA ADMINISTRATION

4.3.1: Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. (Not Graded)

RATIONALE

The correlation between the volume of contrast media administered and the risk of CI-AKI has been recognized.⁴³³ In the vast majority of papers dealing with CI-AKI after coronary procedures, contrast-media doses are only expressed in volumes. The Work Group feels that such expression can be misleading, since commercially available contrast-media concentrations range from 140 to 400 milligrams of iodine per milliliter, a difference with almost a factor of 3. The Work Group recommends, therefore, that the dose of contrast medium should be better expressed in relation to both volume and concentration, e.g., grams iodine, which also directly relates to the diagnostic capacity, the primary purpose of the contrast medium. Such “double” expression would also facilitate the comparison between different studies on epidemiology and prognosis of CI-AKI.

It is well known that, when measuring the plasma clearance of a GFR marker (e.g., with the contrast medium iohexol), the AUC is directly related to the dose of iohexol and inversely related to the GFR. Thus, by mathematically estimating the AUC and knowing the injected iodine dose, the GFR can be calculated by $\text{dose} \div \text{AUC}$. Thus, $\text{AUC} = \text{dose} \div \text{GFR}$, and AUC is directly related to the systemic exposure of a drug, including the contrast medium, which, in turn, is mostly correlated with its efficacy and toxicity.⁴³⁴ An interesting experimental study⁴³⁵ investigated the correlation between the calculated dose to CrCl ratio and

the experimentally measured AUC for the contrast agent iodixanol. The experimentally determined AUC data correlated highly with the dose:CrCl ratio. This ratio could thus be a rapid and accurate way to estimate AUC for an iodinated contrast medium, without the need for multiple blood samples.

A recent study by Nyman *et al.*⁴³⁶ in patients undergoing coronary angioplasty calculated the probability of CI-AKI (SCr rise > 0.5 mg/dl [> 44.2 $\mu\text{mol/l}$] or oliguria/anuria) at various eGFR levels based on g-I (grams iodine)/eGFR ratios of 1:2, 1:1, 2:1, and 3:1. At a ratio < 1 , the risk of CI-AKI was 3%, while it was 25% at a ratio ≥ 1 . This, and other preliminary studies, indicate that a g-I/GFR ratio < 1 may be relatively safe in a patient without multiple risk factors.^{436–438}

Finally, the association between absolute and body weight- and SCr-adjusted contrast-media volume, CI-AKI incidence ($\geq 25\%$ SCr increase), and clinical outcome was prospectively investigated in patients with acute MI.⁴³⁹ For each patient, the maximum contrast-medium dose was calculated according to the formula $(5 \times \text{body weight [kg]}) \div \text{SCr}$, and the contrast-medium ratio—defined as the ratio between the contrast-medium volume administered and the maximum dose calculated—was assessed. Development of CI-AKI was associated with both contrast-medium volume and ratio. Additional radiological measures to reduce CI-AKI can be found in Table 16.

Route of administration of contrast media

The risk of CI-AKI appears to be greater after arterial compared to venous administration of contrast media. Indeed, in the rare studies where an appropriate control group without contrast media was included, no significant difference was observed in the rate of CI-AKI between the patients who received i.v. iodinated contrast media and the control subjects who did not.^{440–442} Thus, the risk of CI-AKI with i.v. contrast medium is probably very low. CI-AKI reportedly occurs after i.v. contrast-medium injection for CT in only 4% of patients with CKD.⁴⁴³ Katzberg and Lamba⁴⁴⁴ summarized the six studies on CI-AKI after i.v. contrast-medium administration in patients at risk and all suffering from moderate CKD. The overall incidence of CI-AKI in these studies, using the current generation of low-osmolar contrast media, was about 5%.

Given the logistic challenges in the outpatient setting, the use of specific prophylactic measures prior to administration of i.v. contrast media could be limited to those subjects who are at higher levels of baseline risk than they would be when an i.a. procedure was planned.⁴⁴⁵ This conclusion, may

Table 16 | Additional radiological measures to reduce CI-AKI*Some CT strategies in patients at risk of CI-AKI*

- Perform CT, when possible, without contrast media; scrutinize the examination and discuss with the referral physician-surgeon before deciding on the need for contrast media.
- Dosing per kilogram body weight to reduce the amount of contrast media is needed in thin patients.
- Adapt injection duration to scan duration when performing CT-angiography, so that the injection is not still running when the scan is finished.
- Use a saline chaser to decrease the amount of contrast media, by using the contrast medium that otherwise would remain in the dead space of the arm veins; this may save 10–20 ml of contrast media.
- Use 80 kVp; contrast-medium dose may be reduced by a factor of 1.5–1.7 compared to the dose used at 120 kVp since iodine attenuation increases, and combine with increased tube loading (mAs) to maintain signal-to-noise ratio.
- Further reduction of contrast media may be instituted in patients with known decreased cardiac output (not unusual in patients with renal impairment) undergoing CT-angiographic studies.

Some angiographic strategies in patients at risk of CI-AKI

- Use biplane when appropriate.
- Avoid test injections; the same amount may be enough for a diagnostic digital-subtraction angiography run.
- Scrutinize each series before performing the next; avoid unnecessary projections.
- Decrease kilovoltage in a thin patient; a lower iodine concentration may be used.
- Assess the physiologic significance of a stenosis by measurement of translesional pressure gradient and fractional flow reserve, a technique well accepted and validated for the coronary circulation. For different arterial beds, perform manometry of a questionable stenosis instead of multiple projections.
- Avoid ventriculography; echocardiography (and “echo contrast”) is always a reasonable alternative.
- Use plasma isotonic contrast-media concentrations for renal artery injections.
- When renal artery stenosis is suspected, map the origin of major renal arteries with noninvasive procedures (e.g., CT without contrast media) for proper initial renal angiographic projections to avoid unnecessary runs, or perform primary manometry.
- CO₂ may be used as contrast medium in venous examinations and below the diaphragm for arterial examinations or alternatively use iodinated contrast media with the same contrast effect, i.e., about 40 mg iodine per milliliter.
- Since the contrast effect of 0.5 M Gd-contrast media has been regarded as diagnostic by many investigators (coronary, renal, aortofemoral arteriography, etc.), iodinated contrast media may be diluted to the same density, i.e., about 75 mg iodine per milliliter.
- Use selective or superselective catheterizations when appropriate, e.g., “single leg run-off”.
- Reduce aortic flow and amount of contrast medium by temporal occlusion of femoral arteries with tourniquets when performing aortography.

Gd, gadolinium; kVp, peak kilovoltage.

however, be too optimistic when applied to critically ill patients undergoing emergency CT scans.³⁹⁵

The majority of the literature covering CI-AKI and its prevention involves i.a. iodinated contrast-medium administration.^{445,446} The higher risk of CI-AKI after i.a. administration is probably due to the more direct exposure of the kidneys to contrast media,⁴⁴⁷ or to the fact that, in general, i.a. contrast-media examinations are performed in patients who carry a higher risk.

RESEARCH RECOMMENDATIONS

- Randomized trials should explore whether there is need for discontinuation of ACE-I and/or ARBs in patients at risk for CI-AKI.
- Additional studies are needed to better determine the exact relationship between the dose of contrast media and the risk for CI-AKI.

SELECTION OF A CONTRAST AGENT

4.3.2: We recommend using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media in patients at increased risk of CI-AKI. (1B)

RATIONALE

This recommendation is supported by the summary tables of the different RCTs and on the evidence profile tables (Suppl Tables 19–21).

High-osmolar vs. iso-osmolar or low-osmolar contrast media

The recommendation to avoid high-osmolar contrast media is based on older literature, since recent RCTs comparing high- vs. low- and iso-osmolar iodine-based contrast media are not available. In addition, high-osmolar contrast media have virtually been abandoned in modern radiological units. Both the review of Goldfarb *et al.*,⁴⁴⁸ and the meta-analysis of Barrett and Carlisle combining 24 randomized studies⁴⁴⁹ suggest that the risk of CI-AKI is similarly low with high-osmolar and low-osmolar agents among otherwise stable patients with normal renal function, but that in contrast to high-osmolar contrast media, low-osmolar contrast media are less nephrotoxic in patients with pre-existing kidney function impairment.

Low-osmolar vs. iso-osmolar contrast media

The present hotly debated question is whether iso-osmolar contrast media are safer than low-osmolar contrast media in high-risk patients. This question has been the subject of a number of randomized trials as well as systematic reviews and meta-analyses (Suppl Tables 19–21).

We separated studies meeting our inclusion criteria (see Chapter 1.2) into those administering i.a. or i.v. contrast media. We used the general definitions of CI-AKI provided in the studies (an increase in SCr by >25% or 0.5 mg/dl [44.2 μmol/l]) occurring within 72 hours after contrast-medium administration, in the absence of an alternative etiology for the decrease in kidney function.

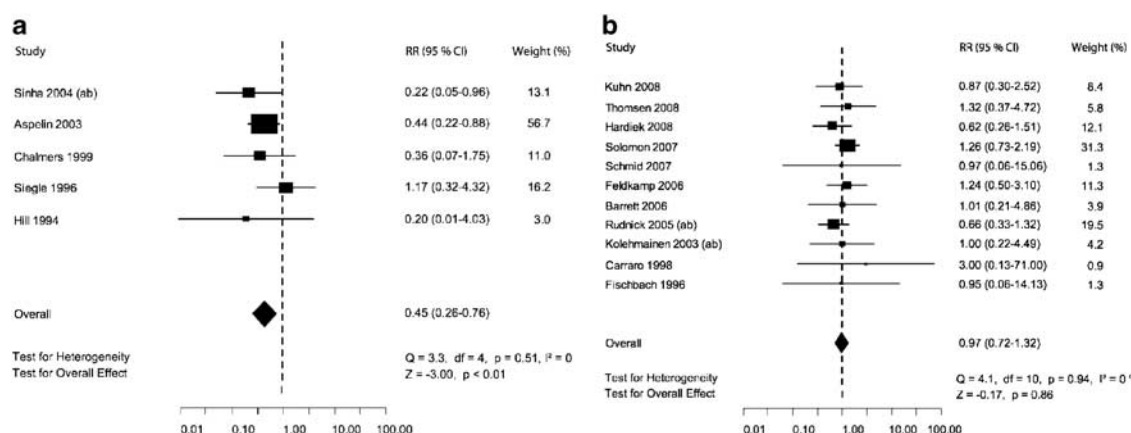


Figure 14 | Risk for contrast-induced nephropathy. (a) Iodixanol vs. iohexol and risk for contrast-induced nephropathy; **(b)** iodixanol vs. nonionic low-osmolar contrast media other than iohexol and risk for contrast-induced nephropathy. Reprinted from Heinrich MC, Haberer L, Muller V *et al.* Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low osmolar contrast media: meta-analysis of randomized controlled trials. *Radiology* 2009; 250: 68-86 with permission, copyright 2009, from Radiological Society of North America⁴⁵⁷; accessed <http://radiology.rsna.org/content/250/1/68.long>

In total, 14 RCTs fulfilling the search criteria were found. Ten RCTs were found with i.a. and four RCTs with i.v. injection, respectively (Suppl Tables 19-21). There is only moderate quality of evidence and overall, no benefit—or, at least, no consistent benefit—was found of nonionic iso-osmolar (iodixanol) contrast media compared to low-osmolar ionic or nonionic contrast media. In eight studies comparing contrast media given i.a.^{401,450-456} some showed superiority of iso-osmolar contrast media (iodixanol), compared to iohexol⁴⁵⁰ and iopromide.⁴⁵⁵ There was no difference when iodixanol was compared to iopamidol,^{401,452} iopromide,^{451,453} and ioversal.⁴⁵⁶

The most recent prospective, multicenter, randomized, double-blind study compared the renal effects of iodixanol to the nonionic, low-osmolar agent iopamidol, in 526 subjects with CKD and diabetes mellitus undergoing diagnostic and/or therapeutic coronary angiography.⁴⁵⁴ The overall CI-AKI incidence was 10.5% (11.2% in the iodixanol arm and 9.8% in the iopamidol arm, NS). The volume of contrast medium, volume of saline administered, frequency of coronary interventional procedures, and severity of baseline kidney disease and of diabetes mellitus were similar between treatments.

Finally, a recent meta-analysis⁴⁵⁷ (Figure 14) analyzed studies comparing iodixanol with low-osmolar contrast media. The pooled RR was 0.68 (95% CI 0.46-1.01; $P = 0.06$). In studies that included patients with normal renal function after i.a. contrast-media administration, the RR was 0.82 (95% CI 0.45-1.51; $P = 0.53$). In the studies that included only patients with decreased kidney function after i.a. contrast-media administration, the RR was 0.59 (95% CI 0.33-1.07; $P = 0.08$). However, in all three studies in which iohexol was the low-osmolar contrast medium used, the risk of CI-AKI was significantly lower with iodixanol (RR 0.38; 95% CI 0.21-0.68; $P < 0.01$). In contrast, the risk of CI-AKI did not significantly differ in the two studies in which

iodixanol was compared to other low-osmolar contrast agents (RR 0.95; 95% CI 0.50-1.78; $P = 0.86$). Iodixanol is thus not associated with a significantly reduced risk of CI-AKI compared to the low-osmolar contrast media pooled together. However, in patients with decreased kidney function, iodixanol is associated with a reduced risk of CI-AKI compared to iohexol.

The clinical heterogeneity between all these studies, as far as basal kidney function and prevalence of diabetes mellitus are concerned, hampers the ability to compare the results across studies, but can widen the applicability of consistent findings across different risk groups provided the mechanisms of contrast-induced nephrotoxicity are the same. One should note, also, that in all these studies different definitions of CI-AKI have been used and that the timing of SCR measurements after contrast-media injection was not uniform. It has been shown that different time-points for the measurement of CI-AKI can give different results.⁴⁵⁸ One may expect that those studies with a standardized and simultaneous measurement of renal function between the two arms are probably the most conclusive. Finally, different types and amounts of volume expansion and different pharmacological preventive strategies have been used throughout the studies, making conclusive comparisons virtually impossible.

i.a. Iodixanol vs. ioxaglate

Two studies fulfilled our inclusion criteria; one study⁴⁵⁹ showed a superiority of iodixanol vs. ioxaglate, but this was not confirmed in the study by Mehran *et al.*,⁴⁶⁰ who found no difference between these two contrast agents. Although overall the number of patients is substantial, there is heterogeneity among the comparators with which iodixanol has been compared. In addition, the cost of iodixanol is probably higher than the cost of most of the low-osmolar contrast agents. No studies comparing a possible difference

among low-osmolar contrast media have been performed. Based on evidence profiles (Suppl Tables 19 and 20) and the most recent meta-analysis⁴⁵⁷ (Figure 14) of the studies comparing i.v. administration of iso- vs. low-osmolar contrast media, the Work Group found no evidence to recommend a preference for either type of agent.

i.v. Administration

There are four studies following i.v. injections fulfilling our inclusion criteria: Barrett *et al.*,⁴⁴³ Kuhn *et al.*,⁴⁶¹ Thomsen *et al.*,⁴⁶² and Nguyen *et al.*⁴⁶³ The overall conclusion, based on the evidence profile summarized in Suppl Table 20 comparing i.v. iso- vs. low-osmolar contrast media, is that there is no benefit for the nonionic iso-osmolar agent (iodixanol); the overall quality of the evidence is moderate. This conclusion is supported by the above-mentioned recent meta-analysis⁴⁵⁷ which, in seven studies comparing i.v. contrast-media administration with iodixanol vs. low-osmolar contrast media, showed no statistically significant difference for CI-AKI (RR 1.08; 95% CI 0.62–1.89; $P=0.79$). Subgroup analysis did not show superiority of any agent in studies of individuals with normal kidney function (RR 1.12; 95% CI 0.35–3.65; $P=0.85$) or in studies of individuals with reduced kidney function (RR 1.07; 95% CI 0.56–2.02; $P=0.84$).

In head-to-head comparisons with different low-osmolar agents, iodixanol has been shown to be superior to

iopromide, but not to iopamidol and iomeprol. It is, however, difficult to determine whether this is simply due to spurious findings in a smaller number of comparisons, or due to true differences between low-osmolar agents. Until better head-to-head comparative studies among the different contrast media agents are available, the Work Group is unable to draw definite conclusions on the selection of iso-osmolar vs. low-osmolar contrast media.

RESEARCH RECOMMENDATION

- Additional studies with head-to-head comparisons among the different contrast media should be performed in order to draw definite conclusions on the selection of iso-osmolar vs. low-osmolar contrast media. A more uniform definition of CI-AKI, as suggested in this guideline, should be used as the end-point.

SUPPLEMENTARY MATERIAL

Supplementary Table 19: Evidence profile of RCTs examining the effect of intrarterial isosmolar vs. low osmolar contrast agent on the prevention of CI-AKI.

Supplementary Table 20: Evidence profile of RCTs examining the effect of intravenous isosmolar vs. low osmolar contrast agent on the prevention of CI-AKI.

Supplementary Table 21: Summary table of RCTs examining the effect of isosmolar vs. low osmolar contrast agent on the prevention of CI-AKI. Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 4.4: Pharmacological prevention strategies of CI-AKI

FLUID ADMINISTRATION

Extracellular volume expansion at the time of radiocontrast-media administration may serve to counteract both the intrarenal hemodynamic alterations and the direct tubulotoxic effects that play a role in the pathophysiology of CI-AKI. Neurohumoral effects of volume expansion that may attenuate radiocontrast-induced medullary hypoxia include suppression of vasopressin as well as inhibition of the renin-angiotensin axis; but an increased synthesis of vasodilatory renal prostaglandins may also play a role.⁴⁶⁴

Volume expansion may also directly reduce cellular damage by dilution of the contrast medium, particularly in the medullary tubular segments. Likewise, an effect of radiocontrast media to increase tubular fluid viscosity may be diminished by intravascular volume expansion.⁴⁶⁵ It is important to note that these potentially attenuating effects of volume expansion are speculative, and the precise mechanisms by which volume expansion protects against CI-AKI remain unknown.

4.4.1: We recommend i.v. volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no i.v. volume expansion, in patients at increased risk for CI-AKI. (1A)

RATIONALE

Despite the recognition of volume depletion as an important risk factor for AKI, there are no RCTs that have directly evaluated the role of fluids vs. placebo in the prevention of AKI. However, RCTs have compared different fluids and have combined fluids with other interventions.¹⁹¹ Furthermore, comparisons between outcomes seen in these trials¹⁹¹ and historical untreated control subjects⁴⁶⁶ suggest a large benefit from fluids. In particular, volume expansion and treatment of dehydration are well-established interventions in the prevention of CI-AKI. A recent propensity analysis, however, noted that strategies to prevent CI-AKI are implemented rather nonuniformly.⁴⁶⁷ Pre- and post-contrast-media administration i.v. fluids were given to only 264 of 660 study patients (40.0%), more commonly with coronary angiography than with CT (91.2% vs. 16.6%). Other preventive measures, such as administration of NAC or discontinuation of NSAIDs, were equally rarely applied. Only 39.2% of patients received NAC, while only 6.8% of patients were instructed to discontinue NSAIDs. In a propensity analysis, the use of i.v. fluids was associated with a reduced rate of CI-AKI. The

incidence of CI-AKI was lowest following CT (range, 0.0–10.9%) and was highest following noncoronary angiography (range, 1.9–34.0%).

The fluids that have been tested in the prevention of CI-AKI are hypotonic saline (0.45%), isotonic saline (0.9%) and isotonic sodium bicarbonate. The interpretation of all these studies is hampered by the fact that not all other risk factors (susceptibilities) for CI-AKI were excluded or considered in every study (i.e., age of the patient, presence of CKD and/or diabetes prior to contrast-media administration, type and dose of contrast agent, associated therapy with NAC, and other risk factors [see Chapter 2.2]).

There is no clear evidence from the literature to guide the choice of the optimal rate and duration of fluid infusion in CI-AKI prevention, but most studies suggest that the fluids should be started at least 1 h before and continued for 3–6 hours after contrast-media administration. A “good” urine output (>150 ml/h) in the 6 hours after the radiological procedure has been associated with reduced rates of AKI in one study.⁴⁶⁸ Since not all of i.v. administered isotonic crystalloid remains in the vascular space, in order to achieve a urine flow rate of at least 150 ml/h, ≥ 1.0 – 1.5 ml/kg/h of i.v. fluid has to be administered for 3–12 hours before and 6–12 hours after contrast-media exposure.

Mueller *et al.*⁴⁶⁹ found that i.v. 0.9% saline solution, compared to 0.45% saline solution in dextrose, in 1620 patients undergoing coronary angiography significantly reduced CI-AKI. The sustained administration of isotonic saline before and after radiocontrast injection seems, thus, to be more protective than equivalent volumes of hypotonic saline.⁴⁶⁴ Although the mechanism by which sodium bicarbonate, beyond its volume-expanding effects, might further reduce CI-AKI remains poorly defined, it has been postulated that sodium bicarbonate infusion may decrease generation of free radicals mediated by the Haber-Weiss reaction by increasing tubular pH. The Haber-Weiss reaction is most active at lower pH levels.⁴⁷⁰ Sodium bicarbonate infusion may also scavenge the potent oxidant peroxynitrate, produced via a nitric oxide-mediated pathway.⁴⁷¹ Reactive oxygen species activate cytokine-induced inflammatory mediators, resulting in damage to proximal tubular cells,⁴⁷² and it is likely that the activation of these mediators is influenced by tissue hypoxia and intracellular medullary acidosis.⁴⁷³

It is worth noting that, compared to i.v. bicarbonate, the combination of oral acetazolamide inducing an alkaline urine, plus i.v. saline, was more effective for the prevention of

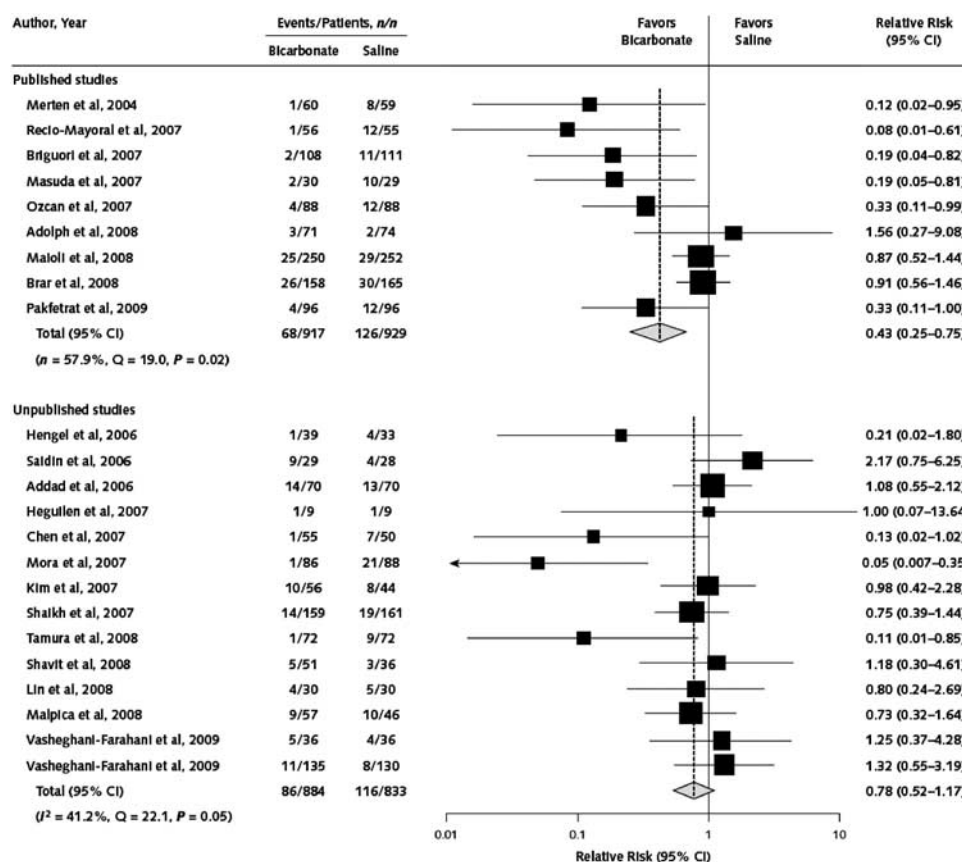


Figure 15 | Bicarbonate vs. saline and risk of CI-AKI. Reprinted from Zoungas S, Ninomiya T, Huxley R *et al.* Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med* 2009; 151: 631–638 with permission from American College of Physicians⁴⁸¹; accessed <http://www.annals.org/content/151/9/631.full>

CI-AKI than saline alone, in a relatively small study in children with stable chronic renal failure (CRF).⁴⁷⁴ It could also be hypothesized that sodium bicarbonate has a stronger impact in lowering the intratubular viscosity caused by the contrast medium, compared to isotonic saline, because it causes less tubular sodium reabsorption than saline.

Sodium bicarbonate solutions have been tested in the prevention of CI-AKI in comparison with isotonic saline, either with or without NAC. A number of systematic reviews on the role of sodium bicarbonate compared to isotonic saline in the prevention of CI-AKI are available.^{475–481}

The most recent and probably the most complete systematic review⁴⁸¹ analyzed MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from 1950 to December 2008; conference proceedings; and ClinicalTrials.gov, without language restriction (Figure 15). This systematic review included RCTs of i.v. sodium bicarbonate that prespecified the outcome of CI-AKI as a 25% increase in baseline SCr concentration or an absolute increase of 0.5 mg/dl (44.2 μ mol/l) after contrast-media administration. Twenty-three published and unpublished trials with information on 3563 patients and 396 CI-AKI events were included. The pooled RR was 0.62 (95% CI 0.45–0.86), with evidence of significant heterogeneity across

studies. Some heterogeneity was due to the difference in the estimates between published and unpublished studies: RR 0.43 (95% CI 0.25–0.75) vs. 0.78 (95% CI 0.52–1.17), respectively. Meta-regression showed that small, poor-quality studies that assessed outcomes soon after contrast-media administration were more likely to suggest the benefit of bicarbonate ($P < 0.05$ for all). No clear effects of treatment on the risk for dialysis, heart failure, and total mortality were identified.

Suppl Tables 22 and 23 summarize the evidence from RCTs where isotonic bicarbonate was compared to isotonic saline alone, without concomitant other “preventive” interventions. In all studies, a minimum of 50 patients in both arms and publication as full paper were required for inclusion in the tables. Only three studies directly compared isotonic bicarbonate to isotonic saline.^{470,482,483} In a fourth study by Brar *et al.*,⁴⁸⁴ NAC was included in 47% and 46% of the patients in both arms of the study (bicarbonate vs. saline), respectively. The first study was a small single-center RCT⁴⁷⁰ enrolling 119 patients with stable SCr of at least 1.1 mg/dl (97.2 μ mol/l), randomized to either infusion of isotonic saline or isotonic sodium bicarbonate before and after contrast-media administration. CI-AKI (defined as an increase of 25% in SCr from baseline within 48 hours)

developed in 1.7% in the bicarbonate group, compared to 13.6% in the saline solution group.

Ozcan *et al.*⁴⁸³ included three prophylactic regimens: infusion of sodium bicarbonate, sodium chloride, and sodium chloride plus oral NAC (600 mg b.i.d.). The incidence of CI-AKI, defined as an increase in SCr level $>25\%$ or 0.5 mg/dl (44.2 μ mol/l) after 48 hours was significantly lower in the sodium bicarbonate group (4.5%) compared to sodium chloride alone (13.6%, $P=0.036$). After adjusting for the Mehran nephropathy risk score, the risk of CI-AKI significantly reduced with sodium bicarbonate compared to sodium chloride alone (adjusted risk ratio 0.29; $P=0.043$).

By contrast, Adolph *et al.*⁴⁸² did not find differences in CI-AKI between the two fluid regimens on day 1 after angiography; even on day 2, most parameters were similar in both groups. In none of the above-mentioned studies was there need for RRT.

Finally, a recent but retrospective study⁴⁸⁵ defined CI-AKI as an increase in SCr $\geq 25\%$ within 48 hours of receiving contrast media, and compared sodium bicarbonate to normal saline in patients exposed to cardiac angiography. One group of patients ($n=89$) received prophylactic bicarbonate; a second group, normal saline ($n=98$). The patients in the bicarbonate group had more severe renal disease with higher baseline SCr (1.58 ± 0.5 mg/dl; 140 ± 44.2 μ mol/l) vs. (1.28 ± 0.3 mg/dl; 113 ± 26.5 μ mol/l), $P=0.001$ and a lower eGFR, compared to the normal saline group. After contrast-media exposure, there was significant drop in eGFR (6.4%) and increase in SCr (11.3%) in the normal saline group and no significant change in the bicarbonate group. Three patients (3.4%) in the bicarbonate group, as opposed to 14 patients (14.3%) in the normal saline group, developed CI-AKI ($P=0.011$). Two patients in the normal saline group and none in the bicarbonate group needed dialysis. This study suggests that the use of i.v. sodium bicarbonate is more effective than normal saline in preventing CI-AKI.

Three studies compared bicarbonate and saline solutions associated with the administration of NAC in both study arms.^{486–488} Recio-Mayoral *et al.*⁴⁸⁸ conducted a prospective single-center RCT in 111 consecutive patients with acute coronary syndrome undergoing emergency angioplasty. One group of patients received an infusion of sodium bicarbonate plus NAC started just before contrast-media injection and continued for 12 hours after angioplasty. The second (control) group received the standard fluid protocol consisting of i.v. isotonic saline for 12 hours after angioplasty. In both groups, two doses of oral NAC were administered the next day. A SCr concentration >0.5 mg/dl (>44.2 μ mol/l) from baseline after emergency angioplasty was observed in 1.8% in the bicarbonate group and in 21.8% of the saline group. Mortality and need for RRT were not significantly different between both groups. Briguori *et al.*⁴⁸⁶ randomized 326 CKD patients (SCr ≥ 2 mg/dl [≥ 177 μ mol/l] and/or eGFR <40 ml/min per 1.73 m²), and referred for coronary and/or peripheral procedures to three different protocols:

prophylactic administration of 0.9% saline infusion plus NAC ($n=111$), sodium bicarbonate infusion plus NAC ($n=108$), and 0.9% saline plus ascorbic acid plus NAC ($n=107$). CI-AKI was defined as an increase of $\geq 25\%$ in the SCr concentration 48 hours after the procedure. CI-AKI occurred in 9.9% of the saline plus NAC group, in 1.9% of the bicarbonate/NAC group ($P=0.019$ vs. saline plus NAC group), and in 10.3% of the saline plus ascorbic acid plus NAC group ($P=1.00$ vs. saline plus NAC group). There was no difference in mortality nor in need for RRT among the different groups. While these two studies suggest that isotonic bicarbonate may provide greater benefit than isotonic saline, either in association with NAC or not, neither study can be considered conclusive.

Maioli *et al.*⁴⁸⁷ prospectively compared the efficacy of sodium bicarbonate vs. isotonic saline in addition to NAC in a larger population of 502 patients with an estimated CrCl <60 ml/min, and undergoing coronary angiography or intervention. CI-AKI was defined as an absolute increase of SCr ≥ 0.5 mg/dl (≥ 44.2 μ mol/l) measured within 5 days. CI-AKI occurred in 10.8%; 10% were treated with sodium bicarbonate and 11.5% with saline. In patients with CI-AKI, the mean increase in creatinine was not significantly different in the two study groups. Based on this last prospective study, bicarbonate does not seem to be more efficient than saline. Furthermore, a retrospective cohort study at the Mayo Clinic assessed the risk of CI-AKI associated with the use of sodium bicarbonate, NAC, or the combination. Surprisingly, i.v. sodium bicarbonate was associated with an increased incidence of CI-AKI.⁴⁸⁹

While one might take the position that, if in doubt, one should choose the regimen that is potentially superior, the Work Group also considered the potential harm. In addition, isotonic bicarbonate solutions are usually composed by adding 154 ml of 8.4% sodium bicarbonate (i.e., 1 mmol/ml) to 846 ml of 5% glucose solution, resulting in a final sodium and bicarbonate concentration of 154 mmol/l each. Since this mixing of the solution is often done at the bedside or in the hospital pharmacy, there is the possibility for errors leading to the infusion of a hypertonic bicarbonate solution. The potential for harm from dosing errors, and the added burden from preparation of the bicarbonate solution, has to be taken into account in clinical practice when making a choice between using bicarbonate rather than standard isotonic saline solutions. Taken together, the Work Group concluded that there is a possible but inconsistent benefit of bicarbonate solutions based on overall moderate-quality evidence (Suppl Table 22). As discussed above, the potential of harm and the additional burden for preparing the bicarbonate solutions led the Work Group not to express a preference for or against one solution (isotonic saline or isotonic bicarbonate). Thus, either can be used for the prevention of CI-AKI.

4.4.2: We recommend not using oral fluids alone in patients at increased risk of CI-AKI. (1C)

RATIONALE

Oral volume expansion may have some benefit, but there is not enough evidence to show that it is as effective as i.v. volume expansion.⁴⁹⁰ One small RCT of 53 patients⁴⁹¹ who underwent nonemergent cardiac catheterization found that i.v. volume expansion with saline was more effective than unrestricted oral fluid intake. A more recent trial⁴⁹² examined the effects of oral volume intake on renal function in 180 patients with preserved renal function referred for coronary CT angiography. The patients were divided into two groups: 106 subjects with an increase in SCr after coronary CT angiography; and 74 without. Significant correlations were observed between the amount of oral fluid intake and the percentage changes in SCr as well as the absolute changes in eGFR. In multiple regression analysis, the amount of oral fluid intake was the only independent predictor for an increase in SCr. However, a recent study compared oral fluids (water with or without bicarbonate) to i.v. fluids (isotonic saline or bicarbonate) and did not find differences in incidence of CI-AKI patients with mild CKD. If confirmed in larger studies, this regimen could offer an equivalent and more practical approach in preventing a decline in renal function after contrast exposure, without accruing additional delay in hospital days or in-hospital mortality.⁴⁹³

ROLE OF NAC IN THE PREVENTION OF CI-AKI

4.4.3: We suggest using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (2D)

RATIONALE

NAC—in many, but not all, studies—has been shown to have a protective effect on CI-AKI when administered before the onset of renal insult; for a review, see McCullough.⁴⁹⁴ In addition, NAC is inexpensive and appears to be safe, although it may have some detrimental effects on myocardial and coagulation function.^{371–373} The “safety” of NAC should further be amended, particularly when high i.v. doses are used, as in some of the RCTs in CI-AKI. When prospectively studied in acetaminophen poisoning, i.v. NAC produced anaphylactoid reactions in up to 48% of participants.³⁷⁴ Although most of these reactions were mild, at least one death has been reported in a patient with asthma.³⁷⁵ It should be noted that the doses used in acetaminophen intoxication are still much higher than in the “high doses” used in CI-AKI prevention trials. In a recent review,⁴⁹⁵ doses of NAC 300 mg/kg i.v. over 21 hours, 980 mg/kg i.v. over 48 hours, and 1330 mg/kg p.o. over 72 hours were mentioned to have been all comparably effective at preventing hepatotoxicity in most uncomplicated early-presenting acute acetaminophen overdoses. Although a variety of doses of NAC has been administered in the prevention of CI-AKI, the i.v. “high doses” used in one study⁴⁹⁶ are mostly 2×1200 mg NAC per day for 2–3 days, far below the doses used in acetaminophen

intoxication. A meta-analysis⁴⁹⁷ of studies using high doses of NAC defined the latter as a daily dose greater than 1200 mg or a single periprocedural dose greater than 600 mg (periprocedural being described as immediately or within 4 hours of the planned contrast exposure). It should also be remembered that no FDA label is available for NAC as a preventive drug of AKI.

Suppl Tables 24 and 25 summarize the quite numerous RCTs where NAC has been compared to placebo on the impact of patient mortality, need for RRT, or prevention of CI-AKI. In most of the studies, i.v. fluids, either with isotonic saline or with isotonic bicarbonate, was used in both arms. Moreover, the impact of NAC on important “hard” patient outcomes, such as all-cause mortality, need for RRT, or doubling of SCr level has only rarely been studied. At present, there is no current evidence that either oral or i.v. NAC can alter mortality or need for RRT after contrast-media administration to patients at risk for CI-AKI. The only study showing a significant decrease in hospital mortality is the three-arm study of Marenzi *et al.*⁴⁹⁸ in patients undergoing primary angioplasty. Overall in-hospital mortality was higher in patients with CI-AKI, defined as a 25% increase in SCr, than in those without CI-AKI (26 % vs. 1 %; $P < 0.001$). Thirteen patients (11%) in the control group died, as did five (4%) in the standard-dose NAC and three (3%) in the high-dose NAC group ($P = 0.02$). All other studies did not show a beneficial effect on mortality (Suppl Table 25). Overall, this evidence was deemed to be of moderate quality and the possible positive effect on mortality dubious.

The effect of NAC on the incidence of CI-AKI is quite variable. As is shown in the evidence profile (Suppl Table 24), the evidence that NAC reduces CI-AKI, as defined in the different trials, comes from studies with rather heterogeneous results; most of the studies were of either high or modest quality. In one study, a protective—even dose-dependent—effect was observed.⁴⁹⁸ In that study, the risk for CI-AKI was reduced by 54.5% in the standard-dose NAC group and by 75.8% in the high-dose NAC group. These findings are in sharp contrast to many other studies showing no effect and, in particular, with the large study of Webb *et al.*,⁴⁹⁹ which was terminated early after enrollment of 487 patients because of a determination of futility by the Data Safety Monitoring Committee. As mentioned earlier, combination studies of NAC with bicarbonate administration⁴⁸⁶ have found a moderate benefit for this combination, compared to the combination of NAC-saline.

As recently remarked by Fishbane,³⁶⁴ most of the studies published on NAC for the prevention of CI-AKI are quite small in size, and meta-analyses have been performed to increase the probability of explaining the full spectrum of utility for NAC. To date, seven out of the 11 meta-analyses that have been published on this subject found a net benefit for NAC in the prevention of CI-AKI.³⁶⁴ However, as pointed out before, marked heterogeneity in the studies, and publication bias must lead to the conclusion that “pooling of data to arrive at a summary estimate for treatment efficacy

should generally be avoided in situations where the trials exhibit significant statistical and/or clinical heterogeneity^{500,501}. A recent prospective RCT⁵⁰² was performed in patients with decreased kidney function ($\text{CrCl} \leq 60 \text{ ml/min}$ and/or SCr level of $\geq 1.1 \text{ mg/dl}$ [$\geq 97.2 \mu\text{mol/l}$]), comparing a high oral dose of NAC with high doses of vitamin C. All patients underwent a coronary angiography. The primary end-point was the maximum increase of SCr level, and the secondary end-point was the incidence of CI-AKI, defined as a relative increase in baseline SCr level of $\geq 25\%$ and/or an absolute increase of $\geq 0.5 \text{ mg/dl}$ ($\geq 44.2 \mu\text{mol/l}$) within 48 hours after contrast-media administration. The maximum increase of SCr level was significantly lower in the NAC group than in the ascorbic acid group ($-0.03 \pm 0.18 \text{ mg/dl}$ [$-2.65 \pm 15.9 \mu\text{mol/l}$] vs. $0.04 \pm 0.20 \text{ mg/dl}$ [$3.54 \pm 17.7 \mu\text{mol/l}$]), respectively ($P = 0.026$). The incidence of CI-AKI tended to be in favor of NAC rather than ascorbic acid, 1.2% vs. 4.4%, respectively, although this difference was not significant ($P = 0.370$). It was concluded that an oral high dose of NAC seemed to be more beneficial than ascorbic acid in preventing CI-AKI, particularly in diabetic patients with pre-existing CKD.

Finally, a randomized, single-blind, controlled trial was recently published to assess NAC effects on CI-AKI and reperfusion injury in ST-segment elevation myocardial infarction (MI) patients undergoing primary angioplasty with moderate contrast-media volumes (between 120–230 ml of an iso-osmolar contrast medium).⁴⁹⁶ The patients undergoing primary angioplasty were randomized to either high-dose NAC (two times 1200 mg/d for 48 hours; or placebo plus fluids). CI-AKI occurred in 14% of the NAC group and in 20% of the placebo group ($P = 0.28$). The myocardial salvage index was also not different between both treatment groups. Activated oxygen protein products and oxidized low-density lipoprotein as markers for oxidative stress were reduced by as much as 20% in the NAC group, whereas no change was evident in the placebo group.

Thus, despite high-dose i.v. NAC reducing oxidative stress, it does not provide an additional clinical benefit, compared to placebo, with respect to CI-AKI and myocardial reperfusion injury in nonselected patients undergoing angioplasty. A recent meta-analysis of all prospective trials of individuals randomized to either orally or i.v. administered high doses of NAC, defined as a daily dose greater than 1200 mg or a single periprocedural dose (within 4 hours of contrast-media exposure) $> 600 \text{ mg}$, was published by Trivedi *et al.*⁴⁹⁷ The overall effect size, assuming a common OR, was 0.46 (95% CI 0.33–0.63) for the occurrence of CI-AKI with the use of high-dose NAC. The results of the more conservative random-effects approach were similar (OR 0.52; 95% CI 0.34–0.78).

Another recently published meta-analysis of RCTs included published trials and conference abstracts (Figure 16).⁵⁰³ The primary and secondary outcomes of interest were CI-AKI, and renal failure requiring dialysis, respectively. Ten RCTs met the inclusion criteria. Nine studies compared combination treatment (bicarbonate and NAC) to NAC and normal saline; one study compared combination therapy to

NAC alone; one study compared combination therapy to NAC with normal saline, and a separate arm with NAC and ascorbic acid. Collectively, combination treatment of NAC with i.v. sodium bicarbonate reduced CI-AKI by 35% compared to the other above-mentioned combinations (RR 0.65; 95% CI 0.40–1.05). However, the combination of NAC plus sodium bicarbonate did not significantly reduce renal failure requiring dialysis (RR 0.47; 95% CI 0.16–1.41). It was concluded that combination prophylaxis with NAC and sodium bicarbonate substantially reduced the occurrence of CI-AKI overall, but not dialysis-dependent renal failure. This paper suggests that combination prophylaxis should be incorporated for all high-risk patients (emergent cases or patients with pre-existing CKD). Most of the studies administered NAC orally; some studies used the i.v. route or even a combination of oral and i.v. There was also a substantial variation in doses and timing of NAC administration.

One additional study was recently published and was thus not included in the meta-analysis discussed above. Koc *et al.*,⁵⁰⁴ investigated the efficacy of prophylactic i.v. NAC and fluids for the prevention of CI-AKI in patients with mild to moderate renal dysfunction ($\text{SCr} \geq 1.1 \text{ mg/dl}$ [$\geq 97.2 \mu\text{mol/l}$] or a $\text{CrCl} \leq 60 \text{ ml/min}$) who were undergoing coronary angiography. A group of patients was assigned to i.v. NAC (bolus of 600 mg twice daily before and on the day of the procedure) plus high-dose normal saline, a second group to only high-dose saline, and a third (control) group received standard saline. Patients in the NAC plus high-dose saline group received an i.v. bolus of 600 mg of NAC twice daily before and on the day of the coronary procedure (total 2.4 g) plus i.v. 0.9% saline 1 ml/kg/h before, on, and after the day of the coronary procedure. Patients in the high-dose arm received the same amount of isotonic saline, while patients in the control group received an i.v. dose of 0.9% saline 1 ml/kg/h for 12 hours before and 12 hours after the coronary procedure. The rate of CI-AKI in the NAC plus high-dose saline group was lower than in the high-dose saline group without NAC. No significant differences in the primary and secondary end-points were found between the high-dose saline and control groups.

In conclusion, based on the evidence tables and even taking the last recent study into account, the overall benefit of NAC is not consistent or overwhelming. On the other hand, oral NAC has a low risk of adverse events and usually a low cost.

THEOPHYLLINE AND FENOLDOPAM IN PREVENTION OF CI-AKI Theophylline

4.4.4: We suggest not using theophylline to prevent CI-AKI. (2C)

RATIONALE

A rationale for the prophylactic use of adenosine antagonists in patients undergoing radiocontrast procedures was

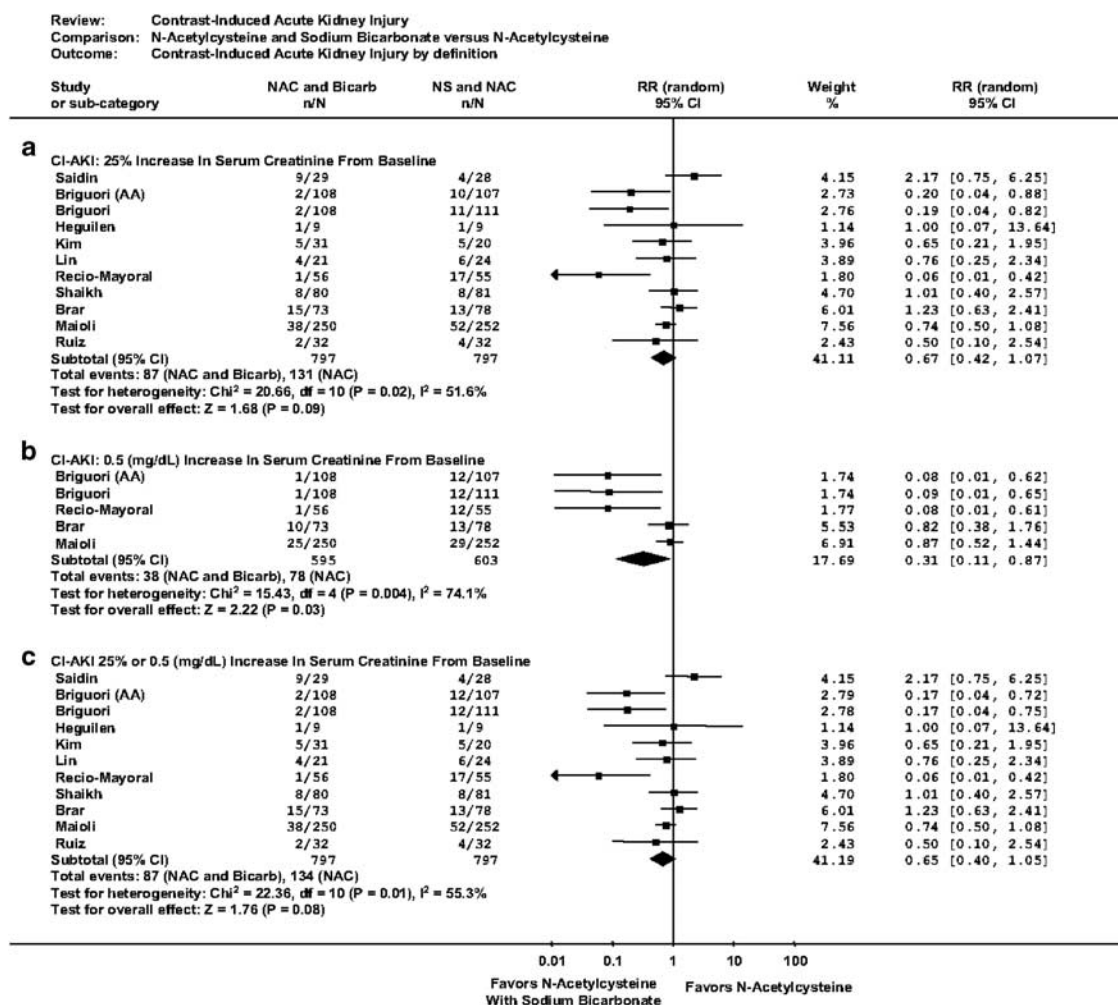


Figure 16 | NAC and bicarbonate vs. NAC for risk of CI-AKI. Reprinted from Brown, JR, Block CA, Malenka DJ *et al.* Sodium bicarbonate plus N-acetylcysteine prophylaxis: a meta-analysis. *JACC Cardiovasc Interv* 2009; 2: 1116–1124,⁵⁰³ copyright 2009, with permission from American College of Cardiology Foundation; accessed <http://interventions.onlinejacc.org/cgi/content/full/2/11/1116>

suggested by results showing increased serum levels and urinary excretion of adenosine occurring after intravascular administration of contrast media.⁵⁰⁵ The efficacy of theophylline in preventing CI-AKI has been addressed by a systematic review and meta-analysis in 2005 (nine RCTs, 585 patients),⁵⁰⁶ and another meta-analysis in 2008 (six RCTs, 629 patients).⁴³² Both meta-analyses indicated a nonsignificant trend toward a renoprotective effect of theophylline prophylaxis. The incidence of CI-AKI tended to be lower (Bagshaw: OR 0.4, CI 0.14–1.16, $P = 0.09$; Kelly: OR 0.49, CI 0.23–1.06, $P = 0.14$), SCr concentrations 48 hours after intervention were significantly lower (-0.17 mg/dl; 95% CI -0.2 to -0.06 mg/dl [-15.0 $\mu\text{mol/l}$, CI -17.7 to -5.30 $\mu\text{mol/l}$]; $P = 0.002$) with theophylline compared to control therapies. However, the overall benefit was small and findings were inconsistent across studies. The benefit attributable to the use of theophylline tended to be less marked in patients receiving iso-osmolar, nonionic contrast media, and in patients undergoing a predefined saline protocol.

Neither meta-analysis included a RCT published in 2006 in 150 contrast-media examinations in 91 patients, in which the renoprotective effects of theophylline, NAC, and the combination of both were directly compared.⁵⁰⁷ All patients had at least one risk factor for developing CI-AKI, and received more than 100 ml of low-osmolar radiocontrast agent. The incidence of CI-AKI was significantly lower with theophylline as compared to NAC pretreatment (2% vs. 12%; $P = 0.045$), and did not differ between theophylline monotherapy and the combination treatment. The renoprotective superiority of theophylline, which was given as a single i.v. 200 mg dose 30 minutes prior to the procedure, was even more significant in patients with pre-existing renal damage as indicated by an SCr > 1.5 mg/dl (> 133 $\mu\text{mol/l}$) ($P = 0.008$). Moreover, a recent study⁵⁰⁸ randomized 217 patients with eGFR between 30 and 60 ml/min who were undergoing coronary angiography to one of three prophylactic treatments: i.v. isotonic saline (1 ml/kg/h for 12 hours before and after contrast media (group 1, $n = 72$); isotonic saline as in group 1 together with NAC (600 mg p.o. twice daily the

preceding day and the day of angiography (group 2, $n = 73$); or isotonic saline and NAC as in group 2 together with 200 mg theophylline orally twice daily for the preceding day and the day of angiography (group 3, $n = 72$). The incidence of CI-AKI (0.5 mg/dl or 44.2 $\mu\text{mol/l}$ SCr increase within 48 hours of intravascular contrast-media injection) was 6.9% in group 1, 9.6% in group 2, and 0% in group 3 ($P < 0.03$), suggesting a beneficial effect of adding theophylline to a standard regimen in the prevention of CI-AKI. Notably, at least in this study, NAC administration had no additive protective effect compared to isotonic saline alone.

A very recent study⁵⁰⁹ randomly assigned patients to prophylactic administration of saline with sodium bicarbonate plus theophylline (either orally or i.v.) or sodium bicarbonate only. Theophylline plus bicarbonate prophylaxis significantly reduced the incidence of CI-AKI (1.6% vs. 7.9%; $P = 0.015$) compared to bicarbonate alone. Theophylline was administered either orally (200 mg b.i.d. starting the day before the contrast administration and continuing for 24 hours thereafter) or i.v. 200 mg in a short infusion before contrast administration and continuing orally at 200 mg b.i.d. for 48 hours. Theophylline prophylaxis significantly reduced the incidence of CI-AKI in moderate and high-risk patients (0% vs. 8.8%; $P = 0.022$ and 9.1% vs. 42.1%; $P = 0.014$, respectively). This study did not mention side-effects of theophylline.

Although these data suggest that preinterventional theophylline administration might be helpful in patients at increased risk for CI-AKI, the possibility of cardiovascular side-effects and the interactions with numerous drugs associated with theophylline^{510,511} should be recognized (Suppl Tables 26 and 27). As can be noted from the evidence profile tables, the evidence is low and the balance of benefits vs. harm is uncertain. In view of the low evidence and the uncertain balance of benefits vs. harm, the Work Group does not support the use of theophylline for prevention of CI-AKI.

Fenoldopam

4.4.5: We recommend not using fenoldopam to prevent CI-AKI. (1B)

RATIONALE

Fenoldopam is a selective dopamine A1 receptor agonist that might theoretically increase blood flow, especially to the renal medulla. Several uncontrolled studies (historical controls, retrospective review) suggested that it is effective in reducing the risk for contrast-induced nephropathy, and the results of a pilot trial were promising (for review, see Stacul *et al.*⁵¹²). However, two prospective randomized trials showed negative results.^{220,513} In the first trial,⁵¹³ patients

were randomized to saline alone or with fenoldopam (0.1 $\mu\text{g/kg}$ per minute for 4 hours before and after the procedure); a third arm was treated with NAC. The incidence of CI-AKI was similar in the fenoldopam (15.7%) and control (15.3%) groups, and there was no benefit over saline alone. A second, larger trial²²⁰ also confirmed the lack of benefit with fenoldopam. In this double-blind trial of 315 patients, all with saline 0.45%, were randomized to fenoldopam (0.05 $\mu\text{g/kg}$ per minute titrated to 0.1 $\mu\text{g/kg}$ per minute) or placebo starting 1 h before the procedure and continuing for 12 hours afterward. There was no significant difference in the incidence of CI-AKI within 96 hours in the two groups (fenoldopam, 33.6%; placebo, 30.1%) or in the rates of dialysis, rehospitalization, or death at 30 days.

Statins in the prevention of CI-AKI

Two recent studies examined the use of statins in the prevention of CI-AKI patients with CKD. In the first study,⁵¹⁴ 31 patients were prospectively randomized to receive atorvastatin 80 mg/d or placebo for 48 hours before and 48 hours after contrast-medium administration. All patients received i.v. saline and oral NAC. CI-AKI occurred in 16 patients (11%) in the placebo group and 15 patients (10%) in the atorvastatin group. Persistent kidney injury, defined as 1-month increase from baseline creatinine value $> 25\%$, was observed in 30% in the placebo group and in 31% in the atorvastatin group. The second study⁵¹⁵ followed 431 patients, 194 of whom were receiving pravastatin treatment for hypercholesterolemia. SCr levels were measured at baseline (preprocedure) and within 48 hours after contrast-medium exposure (peak postprocedure). Logistic regression analysis revealed that pravastatin treatment, preprocedure SCr, and contrast volume were independently related to the decreased risk of CI-AKI. However, such studies are susceptible to the so-called “healthy user effect” where certain groups may have reduced risk, not because of the drug but because of healthier lifestyles, for which use of the medication is a marker. For example, patients taking statins may also be more compliant with other medical-care regimens that may reduce adverse events.

SUPPLEMENTARY MATERIAL

Supplementary Table 22: Evidence profile of RCTs examining effect of i.v. sodium bicarbonate vs. control for the prevention of CI-AKI.

Supplementary Table 23: Summary table of RCTs examining the effect of i.v. sodium bicarbonate on the prevention of CI-AKI.

Supplementary Table 24: Evidence profile of RCTs examining the effect of NAC vs. placebo on the prevention of CI-AKI.

Supplementary Table 25: Summary table of RCTs examining the effect of NAC vs. placebo on the prevention of CI-AKI.

Supplementary Table 26: Evidence profile of RCTs examining the effect of theophylline vs. placebo on the prevention of CI-AKI.

Supplementary Table 27: Summary table of RCTs examining the effect of theophylline vs. placebo on the prevention of CI-AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 4.5: Effects of hemodialysis or hemofiltration

4.5.1: We suggest not using prophylactic intermittent hemodialysis (IHD) or hemofiltration (HF) for contrast-media removal in patients at increased risk for CI-AKI. (2C)

RATIONALE

Contrast media are excreted mainly by glomerular filtration and there is a significant correlation between both total body and renal clearances of contrast media and GFR; the renal excretion of contrast media will thus be delayed in patients with renal failure (for review, see Deray).⁵¹⁶ Contrast media can be efficiently removed from blood by IHD and a single session effectively removes 60–90% of contrast media.^{516,517} On the basis of these observations, several studies have explored the prophylactic value of IHD in patients at high risk, but most of these studies have not demonstrated a reduced incidence of CI-AKI.^{516,518} For example, Vogt *et al.*⁵¹⁸ recorded renal function and other parameters, IHD requirements, and relevant clinical events before and during 6 days after administration of contrast media in 113 patients with a baseline SCr > 2.3 mg/dl (> 203 μ mol/l). Eight out of 55 patients in the prophylactic IHD group and three in the non-IHD group ($P=0.12$), required IHD after contrast-media examination. Reinecke *et al.*⁵¹⁹ performed a prospective single-center trial in 424 consecutive patients with SCr concentrations between 1.3–3.5 mg/dl (115–309 μ mol/l) who underwent elective coronary angiography. Patients were randomized to one of three treatment strategies with all patients receiving pre- and postprocedural fluids: one group received no additional therapy, patients in the second group were hemodialyzed once, and the third group received oral NAC. The frequency of CI-AKI (defined as an increase in SCr ≥ 0.5 mg/dl or ≥ 44.2 μ mol/l) from 48 to 72 hours after catheterization was 6.1% in the fluids-only group, 15.9% with IHD treatment, and 5.3% in the NAC group (intention-to-treat analysis; $P=0.008$). There were no differences between the treatment groups with regard to increased SCr ≥ 0.5 mg/dl (≥ 44.2 μ mol/l) after 30–60 days (4.8%, 5.1%, and 3.1%, respectively; $P=0.700$). Analyses of long-term follow-up (range 63–1316 days) by Cox regressions models of the study groups found quite similar survival rates ($P=0.500$). This large study concluded that IHD, in addition to fluids, for the prevention of CI-AKI provided no evidence for any outcome benefit but showed evidence for probable harm.

A retrospective but important cohort study of 391 patients (age 69 ± 8 years, with chronic renal insufficiency [SCr ≥ 1.3 mg/dl; ≥ 115 μ mol/l]) who underwent cardiac catheterization, also did not find any beneficial preventive effect.⁵²⁰

By contrast, Lee *et al.*⁵²¹ presented a prospective RCT indicating that prophylactic IHD might be useful in patients scheduled for coronary angiography or coronary intervention with severely impaired renal function (baseline CrCl of 13 ml/min per 1.73 m²). Patients were treated with normal saline at 1 ml/kg/h for 6 hours before and 12 hours after contrast-media administration and randomized to receive IHD for 4 hours as soon as possible after angiography or control treatment. Four days after angiography, SCr concentrations were lower in the IHD group compared to the control group. Out of 42 patients, one patient (2%) in the IHD group but 14 (35%) out of 40 patients in the control group required temporary IHD after coronary angiography. Furthermore, none of the 42 patients in the IHD group, but five (13%) out of 40 patients in the control group, required maintenance IHD after discharge from the hospital ($P<0.05$).

A recent meta-analysis of studies using periprocedural extracorporeal blood purification techniques⁵¹⁷ concluded that such treatments did not decrease the incidence of CI-AKI. It could theoretically be anticipated that high-flux membranes used in HF or hemodiafiltration (HDF) modalities should be able to remove contrast media more efficiently than low-flux membranes used in routine IHD. However, recent publications on this topic have added to the controversy about the role of IHD or HF to prevent CI-AKI (Suppl Tables 28 and 29). Marenzi *et al.*⁵²² studied 114 consecutive patients with CRF (SCr concentration > 2 mg/dl or > 177 μ mol/l) who were undergoing coronary interventions. Fifty-eight patients were assigned to either HF starting before the contrast-medium administration and continuing for up to 24 hours after, while 56 patients were treated with isotonic saline at a rate of 1 ml per kilogram of body weight per hour, given in a step-down unit over the same time interval. In-hospital mortality was 2% in the HF group and 14% in the control group ($P=0.02$), and the cumulative 1-year mortality was 10% and 30%, respectively ($P=0.01$). Temporary RRT was required in 25% of the control group and in only 3% of the patients in the HF group. An increase in the SCr concentration of > 25% from the baseline value after the coronary intervention occurred less frequently among patients in the HF group than among the control patients (5% vs. 50%, $P<0.001$). The effective removal of creatinine during HF or IHD makes it difficult to be certain that an observed lower incidence of CI-AKI is not related to the transport removal of creatinine during the procedure.

In a subsequent study, the same authors⁵²³ randomized 92 patients with CKD (CrCl ≤ 30 ml/min) to three different prophylactic treatments: i.v. isotonic saline (control group); i.v. saline for 12 hours before contrast-media exposure,

followed by HF for 18–24 hours after contrast-media exposure; and a third group where HF was performed for 6 hours before and for 18–24 hours after contrast-media exposure. The incidence of CI-AKI (>25% increase in SCr) and the in-hospital clinical course were compared in the three groups. In-hospital mortality was 20%, 10%, and 0%, respectively, in the three groups; IHD was required in nine (30%), 3 (10%), and zero (0%) patients, respectively ($P=0.002$). According to these results, pre-HF is required to obtain the full clinical benefit, suggesting that among different mechanisms possibly involved, high-volume controlled volume expansion before contrast-media exposure plays a major role in prevention. This study further suggests that bicarbonate exposure with HF may ultimately have been the mechanism for the lower CI-AKI incidence (Suppl Table 29). In summary, the evidence profile for IHD vs. HF showed low-quality evidence and an uncertain benefit vs. harm balance of HF/IHD in preventing CI-AKI in patients with severe CKD. Given the costs and logistical difficulties, the use of HF modalities for CI-AKI prevention can only be advocated if future studies will convincingly show clear benefit.

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SUPPLEMENTARY MATERIAL

Supplementary Table 28: Evidence profile of RCTs examining the effect of hemodialysis or hemofiltration on the prevention of CI-AKI.

Supplementary Table 29: Summary table of RCTs examining the effect of hemodialysis or hemofiltration on the prevention of CI-AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php